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September 20, 2005  
Date

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**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

*In re* Application of:  
SASTRY *et al.*

Serial No.: 08/869,386

Filed: 06/05/97

For: COMPOSITIONS AND METHODS FOR  
ELICITING AN IMMUNE RESPONSE

Group Art Unit: 1648

Examiner: Le, Emily M.

Atty. Dkt. No.: UTXC:538/HYL

**SUPPLEMENTAL BRIEF ON APPEAL**

## **I. Real Party in Interest**

The Real Party in Interest is the assignee, Board of Regents of the University of Texas System.

## **II. Related Appeals and Interferences**

There are no related appeals or interferences.

## **III. Status of Claims**

Claims 1-28, 36-40, 46 and 48 are canceled. Claims 29-35, 41-45, 47 and 49 are pending and subject to rejection.

## **IV. Status of Amendments**

An amendment canceling claims 36-40 is filed concurrently herewith to reduce issues for appeal and will presumably be entered.

## **V. Summary of Claimed Subject Matter**

The invention of claim 29 is concerned with method for directly inhibiting HIV entry into a cell comprising the step of contacting said cell with a composition comprising a peptide of 8 to 24 residues comprising the sequence RAFVTIGK (SEQ ID NO:5), wherein said cell is in a human subject. Specification, page 15, lines 23-28; page 17, lines 24-34.

The invention of claim 30 recites that the peptide is 8 residues in length. Specification, page 66, lines 12-33, particularly line 25.

The invention of claims 31-35, concern peptides of 15 residues in length (claim 31), those having the sequence RIQRGPGRAFVTIGK (SEQ ID NO:1) (claim 32), peptides of 24 amino acids in length (claim 33), those having the sequence NNTRKSIRIQRGPGRAFVTIGKIG (SEQ

ID NO:3) (claim 34), and peptides in the form of a multimer (claim 35). Specification, page 66, lines 12-33.

The invention of claims 41–45, 47 are directed to inclusion of the peptides in a pharmaceutically acceptable aqueous medium (claim 41), administration at a dosage range of between about 10 micrograms to about 500 milligrams (claim 42), a dosage range is about 50 micrograms to about 1 milligram (claim 43), a dosage of about 100 micrograms (claim 44), contacting said cell with said composition a second time (claim 45), and administration by injection (claim 47). These are described in the same sections mentioned above, as well as on pages 36 – 40.

Lastly, claim 49 is concerned with a method for directly inhibiting HIV entry into a cell *in vitro* comprising the step of contacting said cell with a composition comprising a peptide of 8 to 24 residues comprising the sequence RAFVTIGK (SEQ ID NO:5). See Example 8 of the specification.

## **VI. Grounds of Rejection to Be Reviewed on Appeal**

The grounds of rejection to be reviewed on appeal include:

Whether the meaning of the term “directly inhibiting” is indefinite under 35 U.S.C. §112, second paragraph.

The rejection of claim 49 as allegedly anticipated by Koito *et al.*

The rejection of the remaining claims as obvious over Haynes *et al.*, US 5,019,387, in view of Koito *et al.*

## **VII. Argument**

### **A. Miscellaneous Issues**

In the subject Action, a number of issues not pertinent to the present appeal have been raised by the Action. Appellants are merely stating here how these issues will be dealt with should Appellants prevail in the present appeal:

#### **1. Priority**

Appellants agree that the present claims are enabled as of and entitled to the September 16, 1992 filing date. Appellants will amend the continuing data accordingly following appeal.

#### **2. Section 112, Second Paragraph Issues**

In the Action, the Examiner requested clarification regarding the identity of SEQ ID NO:3. In this regard it is stated that the Examiner's identification of the sequence on page 4, line 5, of the subject Action is correct. Regarding the Examiner's request for a full and complete sequence listings, such have already been supplied in Applicants' submissions of September 29, 1997.

With regard to claims 43-44, the dependencies of these claims will be changed to address the antecedent basis issue such that these claims will depend from claim 42.

Regarding the issue with respect to claims 31-34, the dependencies of claims 32 and 34 will be changed to address the Examiner's concerns.

Regarding claims 36-40, these claims have been canceled. The issue with respect to claim 43 will be moot upon the change of dependency of this claim.

## **B. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph**

The Action rejects claims 29-45 and 47 under 35 U.S.C. 112, second paragraph, taking the position that it is “unclear the activity that is intended by the limitation ‘directly inhibiting HIV entry into the cell’.”

In response, it is submitted that “directly inhibiting” or “inhibiting” the “entry of HIV into a cell” is clearly explained in the specification and exemplified by the assay described beginning at page 66, line 20, wherein peptides such as the R15K peptide are tested for their ability to directly inhibit the entry of HIV across a cell having an intact cell membrane. This definition is indeed consistent with the excerpt referred to by the Examiner at the top of page 5 of the subject Action.

Furthermore, “directly inhibiting” or “inhibiting” the “entry of HIV into a cell” is distinguished in the present specification from inhibition of syncytia formation, which is described at page 69, lines 8-23, of the specification. As noted, the test for inhibition of syncytia formation involves *pre*-infecting target cells with HIV *followed* by treating them with the peptides and observing whether the peptides reduce the formation of syncytia. Furthermore, at page 37, lines 15-29, particularly lines 28-29, it is clearly denoted that inhibition of HIV infection is intended to be distinct from inhibition of syncytia formation (noting that the reference of Koito *et al.*, which concerned inhibition of syncytia formation, did not test “these peptide [] for their capacity to inhibit HIV infection of cells.”).

It is submitted in light of the foregoing that the claims are acceptable under 35 U.S.C. 112, second paragraph.

**C. Anticipation of Claim 49**

The Action next rejects claim 49 as anticipated by Koito *et al.* reference.

In response, Appellants are entirely unsure as to how the Examiner considers Koito *et al.* to be relevant to anticipate the subject matter of claim 49. At best, Koito *et al.* merely indicates that an R15K peptide inhibits syncytia formation. Nowhere does Koito *et al.* teach inhibition of HIV entry into a cell. Although the Action is short on explanation, it is presumed that the Examiner is taking the position that inhibition of syncytia formation necessarily results in a reduction in viral entry. Yet, there is no evidence of record to demonstrate this to be the case, and there is no demonstration anywhere in Koito *et al.* that virus entry is in any way inhibited. Thus, no *prima facie* rejection has been made.

**D. Obviousness Rejection of Claims**

Lastly, the Action rejects the remaining claims over the combination of Haynes *et al.* with Koito *et al.*

With respect to Haynes *et al.*, the Action concedes that:

1) “[T]he cell used in the method of Haynes *et al.* is from a primate. Haynes *et al.* does not specify the primate as a human subject.” (Action, page 9);

This is particularly relevant in that the claims subject to rejection are all directed to the treatment of human subjects. The Action fails to provide any explanation how studies involved primates are relevant to the present human therapeutic claims.

2) “[T]he mechanism of action that Haynes *et al.* describes for the composition is not the same as that observed by Applicant. Haynes does not describe the mechanism of action as direct inhibition of HIV entry into cells.”

This is also a critical shortcoming in that present claims are specifically directed to a specific mechanism which is admittedly not taught or suggested by Haynes *et al.* Inherency is not an issue in that Haynes *et al.* is concerned with vaccination to induce an immune response – presumably by intradermal or some similar administration – whereas the present invention involves introduction into the bloodstream. Furthermore, Haynes *et al.* concerns producing immunity by inducing an antibody response but says nothing about the present invention which is directed to inhibiting HIV uptake into cells. Furthermore, as mentioned below, the peptides of Haynes *et al.* relied upon by the Examiner are not the same as those set forth in the pending claims, and thus the doctrine of inherency is inapplicable.

The fact remains, Haynes *et al.* admittedly fails to teach or suggest that the presently claimed peptides can inhibit HIV entry into cells.

3) Haynes *et al.* does not specifically disclose the claimed sequence (Action, page 11)

This observation is particularly damning of the Action's rejection. The Action attempts to argue that the peptides of Haynes *et al.* are somehow interchangeable with those of the present claims, but there is no basis recited for such a proposition. Indeed, the principle peptide structures relied upon by Haynes *et al.* can be found in Table I at col. 4 – yet these peptides are totally unrelated to the present R8K peptides! The peptides in Table II do contain an R8K sequence, but the addition of these sequences are merely indicated as “enhancing” the ability to raise type-specific antibodies, as opposed to themselves being able or responsible for achieving an antibody response. Col. 6, lines 11-19.

With respect to the Action's reliance on Koito *et al.* to complete the rejection, Appellants direct the Board to the discussion above with respect to the distinctions between syncytia formation inhibition and inhibition of HIV entry. The foregoing is most notably seen when one looks at the

concentrations of peptide required by Koito *et al.* to demonstrate inhibition of syncytia formation. The relevant Koito *et al.* peptide cited by the Examiner was “NNT24”. As shown in Table 1, this peptide was only active in inhibiting syncytia formation at concentrations of 100  $\mu\text{M}$  and above. However, the present Applicants have demonstrated that the presently claimed peptides are active at exceedingly lower concentrations – on the order of 0.4 to 0.78  $\mu\text{M}$  – more than two orders of magnitude lower concentration!

This finding is indeed of substantial significance. Koito *et al.* states at the top of page 617, col. 1, that “[t]he high concentration (0.03 – 1 mM) needed to inhibit syncytia formation described here suggests that the [clinical] usage might not be practical.” In other words, compositions that are only active at high concentrations such as 30 to 1000  $\mu\text{M}$  (*ie.*, 0.03 – 1 mM) are simply not good candidates for pharmaceuticals. Thus, one of skill would not be motivated from Koito *et al.* to use the peptides it discloses as a pharmaceutical – they are simply too inactive for the purpose of syncytia formation. However, Appellants discovery that such peptides are active at more than a two-log fold lower concentration, by an unrelated mechanism, now demonstrates their clinical promise.

Lastly, Appellants will close by making of record the PTO’s position in this appeal that the utility claimed by Appellants here would not have been believed by one of skill in the art as of the filing date:

The specification provides no probative evidence to support the claimed treatment which would protect humans against HIV infection. The obstacles to treatment development and therapeutic approaches with regard to retroviruses associated with AIDS in humans are well documented in the literature. These obstacles include: 1) the extensive genomic diversity associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus

to “hide” in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus, due to the blood-brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establish that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any vaccine or any immunization treatment or any therapeutic regimen on its face. In order to enable claims to drugs and their uses, either *in vivo* or *in vitro* data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the claims are sufficiently enabled. When the claims are directed to humans adequate animal data would be acceptable in those instances wherein one of ordinary skill in the art would accept the correlation to humans. Thus in order to rely on animal data there must exist an art-recognized animal model for testing purposes. See In re Hartop, 311, F.2d 249, 135 USPQ 419 (CCPA 1962).

Yarchoan *et al.* (J. Enz. Inh., 1992) state that while a number of agents have been found to block HIV binding to the target ell *in vitro*, these agents have generally not shown clear-cut evidence of clinical activity (abstract). Moreover, Gait *et al.* (TIBTECH 1995) discuss the problems associated with protein therapies for HIV and state that they suffer from problems of short serum half-life, poor bioavailability, and rapid clearance. Gait *et al.* also teach that as these problems were overcome, other problems emerged such as sequestration of the drug by serum proteins, drug resistance, and uneven distribution through the body, and that since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters p. 437).

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988). In the instant specification, it is determined that: 1) there are no working examples which suggest the desired results of inhibiting HIV infection *in vivo*, 2) the nature of the invention involved the complex and incompletely understood area of immunity to HIV, 3) the state of the prior art shows that prior treatment methods have been largely ineffective for the intended purpose, 4) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level), and 5) the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by prior failures. In view of all of the above, it is determined that the specification is not commensurate in scope with the claimed invention.

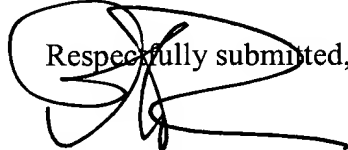
Examiner's Answer dated 4/25/00, paper 21.

We submit that the Action must provide an explanation as to why these observations do not in themselves provide strong evidence of the non-obviousness of the present invention.

In light of the foregoing, the Board is requested to overturn the obviousness rejection.

### **VIII. Conclusion**

Appellants believe that the foregoing remarks fully and appropriately respond to all of the Examiner's rejections. The Board is therefore requested to rule in Appellants favor and overturn the rejections.

Respectfully submitted,  


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## Claims Appendix 1

1. – 28. (Canceled)

29. (Previously presented) A method for directly inhibiting HIV entry into a cell comprising the step of contacting said cell with a composition comprising a peptide of 8 to 24 residues comprising the sequence RAFVTIGK (SEQ ID NO:5), wherein said cell is in a human subject.

30. (Previously presented) The method of claim 29, wherein said peptide is 8 residues in length.

31. (Previously presented) The method of claim 29, wherein said peptide is 15 residues in length.

32. (Previously presented) The method of claim 31, wherein said peptide comprises the sequence RIQRGPGRAFVTIGK (SEQ ID NO:1).

33. (Previously presented) The method of claim 29, wherein said peptide is 24 amino acids in length.

34. (Previously presented) The method of claim 33, wherein said peptide comprises the sequence NNTRKSIRIQRGPGRAFVTIGKIG (SEQ ID NO:3).

35. (Previously presented) The method of claim 29, wherein said peptide is in the form of a multimer.

36. – 40. (Canceled)

41. (Previously presented) The method of claim 29, wherein said composition is dispersed in a pharmaceutically acceptable aqueous medium.

42. (Previously presented) The method of claim 29, wherein said composition is administered at a dosage range of between about 10 micrograms to about 500 milligrams.

43. (Currently amended) The method of claim 40, wherein dosage range is about 50 micrograms to about 1 milligram.

44. (Previously presented) The method of claim 41, wherein said dosage range is about 100 micrograms.

45. (Previously presented) The method of claim 29, further comprising contacting said cell with said composition a second time.

46. (Canceled)

47. (Previously presented) The method of claim 29, wherein said contacting comprises injection of said composition.

48. (Canceled)

49. (Previously presented) A method for directly inhibiting HIV entry into a cell *in vitro* comprising the step of contacting said cell with a composition comprising a peptide of 8 to 24 residues comprising the sequence RAFVTIGK (SEQ ID NO:5).

## **Evidence Appendix 2**

Hayes *et al.*, US 5,019,387, cited in the Office Action dated 6/20/05

Koito et al, cited in the Office Action dated 6/20/05

Excerpt from Examiner's Answer date 4/25/00, paper 21.

### **Related Appeals and Interferences Appendix 3**

None